CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-310

ADMINISTRATIVE DOCUMENTS

~~CORRESPONDENCE~~

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-310 /SE_____ - _____

Drug Alora (estradiol transdermal system) Applicant Watson Laboratories

RPM Samuel Wu Phone 301-827-6416

☒ 505(b)(1)
☐ 505(b)(2) Reference listed drug _____

☐ Fast Track ☐ Rolling Review Review priority: ☒ S ☐ P

Pivotal IND(s) _____

Application classifications:
Chem Class 3 (new formulation)
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary Nov 16, 2001
Secondary Jan 16, 2002

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☒ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☒ AP ☐ AE ☐ NA

- Labeling & Labels
  FDA revised labeling and reviews..... X
  Original proposed labeling (package insert, patient package insert) X
  Other labeling in class (most recent 3) or class labeling..... X
  Has DDMAC reviewed the labeling? Will be in DFS..... ☐ Yes (include review) ☐ No
  Immediate container and carton labels Ar on Tue (4/13)..... _____
  Nomenclature review ..... _____

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☒ is not on the AIP.
  Exception for review (Center Director's memo)..... _____
  OC Clearance for approval..... _____

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) ☒ Materials requested in AP letter
- Post-marketing Commitments — N/A
  - Agency request for Phase 4 Commitments.....
  - Copy of Applicant's commitments .....
- Was Press Office notified of action (for approval action only)? ☐ Yes ☒ No
  - Copy of Press Release or Talk Paper.....
- Patent
  - Information [505(b)(1)] X
  - Patent Certification [505(b)(2)].....
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)].....
- Exclusivity Summary X
- Debarment Statement X
- Financial Disclosure
  - No disclosable information X
  - Disclosable information – indicate where review is located page 9 of clinical review X
- Correspondence/Memoranda/Faxes X
- Minutes of Meetings .....
  - Date of EOP2 Meeting _____
  - Date of pre NDA Meeting _____
  - Date of pre-AP Safety Conference N/A
- Advisory Committee Meeting ..... N/A
  - Date of Meeting .....
  - Questions considered by the committee .....
  - Minutes or 48-hour alert or pertinent section of transcript .....
- Federal Register Notices, DESI documents ..... N/A

CLINICAL INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) X
- Clinical review(s) and memoranda X
- Safety Update review(s) ..... N/A
- Pediatric Information

☒ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
Pediatric Page 23 of the Summary Volume 1.0.1 X
☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☒ Not Applicable

- Statistical review(s) and memoranda X
- Biopharmaceutical review(s) and memoranda X
- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling .....
- Microbiology (efficacy) review(s) and memoranda ..... N/A
- DSI Audits (see filing minutes) ..... N/A
  ☐Clinical studies ☐ bioequivalence studies .....

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda X
- Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A
- DMF review(s) (see CMC reviews) ..... N/A
- Environmental Assessment review/FONSI/Categorical exemption X
- Micro (validation of sterilization) review(s) and memoranda ..... N/A
- Facilities Inspection (include EES report)
  Date completed 3/8, 3/16, 3/20 2001 ..... ☒ Acceptable ☐ Not Acceptable
- Methods Validation (satisfactory, page 21 of CMC Review) ☒ Completed ☐ Not Completed

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PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda X
- Memo from DSI regarding GLP inspection (if any) ..... N/A
- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

The application consists of a total of 38 volumes, each numbered sequentially starting with volume 1.1 and ending with volume 1.38. Information contained in the NDA is identified in the index of the application with an item number, item title, and the corresponding location by NDA volume number. Each item of the NDA has been independently numbered by item volume and page number. Each page of the application includes the section volume number and section page number at the center of the bottom of the page.

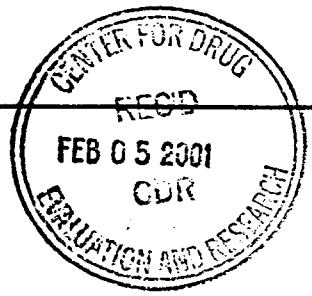
If you have any questions or need any additional information, please feel free to contact me by telephone at (801) 588-6200 or by fax at (801) 583-8135.

Sincerely,

Dorothy A. Frank

Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.



January 12, 2001

John K. Jenkins, M.D., Director
Division of Metabolic and Endocrine
Drug Products (HFD- 510)
CDER, Document Room 14-B-19
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-310 Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

Dear Dr. Jenkins:

In accordance with the Federal Food, Drug, and Cosmetic Act, Watson Laboratories, Inc. is submitting a New Drug Application for Alora Estradiol Transdermal Systems (also referred to as EMTDS in this application).

This application provides clinical data to support an additional indication of "prevention —— of postmenopausal osteoporosis" for currently marketed dosage forms of Alora, as well as Chemistry, Manufacturing, and Controls information and clinical data to support a new 0.025 mg/day dosage strength for the osteoporosis indication.

Three dosage strengths of Alora, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day are currently marketed in accordance with our NDA #20-655 that was approved by the Division of Reproductive and Urologic Drug Products (DRUDP) for the treatment of moderate to severe vasomotor symptoms associated with menopause. Regulations and FDA guidance provide for submission of information contained in this new NDA as a supplement to our approved NDA #20-655. However, FDA has requested submission of a new NDA for their administrative convenience because responsibility for review of information supporting the new indication is not assigned to DRUDP, but to the Division of Metabolic and Endocrine Drug Products.

Mike Jones of the Office of the Center Director also advised us in a teleconference on September 6, 2000 that half of the full user fee amount is required for this submission, as that is the fee that would be required for submission of a supplemental application with clinical data.

This application is being submitted in a combination of paper and electronic files. Complete paper copies of the archival and review copies are provided except for Sections 2, 11, and 12. Section 2 contains Labeling, and is provided in both paper and electronic files. The electronic copy of Section 2 is provided on 1 CDROM at an approximate size of 1 megabyte. Section 11 contains Case Report Tabulations and is provided in the archival copy only, on 1 CDROM at an approximate size of 30 megabytes. Section 12 contains Case Report Forms for Serious Adverse Events and Dropouts Due to Adverse Events and is provided in the archival copy only, on 1 CDROM at an approximate size of 242 megabytes. The software used to check these files for viruses was Norton Antivirus ——

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Watson Laboratories, Inc.	Januay 12, 2001
TELEPHONE NO. (Include Area Code) (801) 588-6200	**FACSIMILE (FAX) Number (Include Area Code)** (801) 583-8135
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 417 Wakara Way Salt Lake City, Utah 84108	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-310

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Estradiol Transdermal System (EMTDS)	Alora® Estradiol Transdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Estra-1,3,5 (10)-triene-3, 17-diol — CODE NAME *(If any)* None

DOSAGE FORM: Transdermal System — STRENGTHS: 0.025, 0.05, 0.075 and 0.1 mg/day — ROUTE OF ADMINISTRATION: Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Add new indication and dosage strength.

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

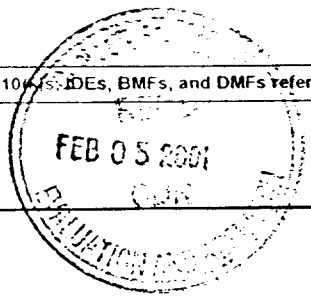
NUMBER OF VOLUMES SUBMITTED 38 — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA #20-655 Alora



This application contains the following items: *(Check all that apply)*

☒	1. Index	
☒	2. Labeling *(check one)*	☒ Draft Labeling ☐ Final Printed Labeling
☒	3. Summary (21 CFR 314.50(c))	
☒	4. Chemistry section	
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
☐	B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
☒	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
☒	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
☒	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
☒	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
☒	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
☒	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)	
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)	
☐	15. Establishment description (21 CFR Part 600, if applicable)	
☒	16. Debarment certification (FD&C Act 306(k)(1))	
☒	17. Field copy certification (21 CFR 314.50(k)(3))	
☒	18. User Fee Cover Sheet (Form FDA 3397)	
☒	19. Financial Information (21 CFR Part 54)	
☐	20. OTHER *(Specify)*	

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Dorothy A. Frank	Dorothy A. Frank, M.S., R.A.C. Director, Regulatory Affairs	01/12/01

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
417 Wakara Way Salt Lake City, Utah, 84108	(801) 588-6200

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Watson Laboratories, Inc.
417 Wakara Way
Salt Lake City, Utah 84108

2. TELEPHONE NUMBER *(Include Area Code)*

(801) 588-6200

3. PRODUCT NAME

Alora

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. Yes

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

—

6. LICENSE NUMBER / NDA NUMBER

N021310

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

TURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Cheri R. Fetterhoff for Dorothy Frank	Dorothy A. Frank Director, Regulatory Affairs	December 30, 2000

FORM FDA 3397 (5/98)

Patent Information

(21 U.S.C. 355(b) or (c))

ORIGINAL

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

19 October, 2001

Division of Metabolic and Endocrine Drug Products (HFD- 510)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Document Room 14-B-19
5600 Fishers Lane
Rockville, MD 20857

21 000 BC
ORIG AMENDMENT

RE: NDA 21-310, Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day – Response to request for CMC information

In response to a telephone inquiry on October 18 of this year by Dr. Elsbeth Chikale regarding the Chemistry review of NDA 21-310, we are providing the following information.

A. Dr. Chikale requested that Watson provide a calculation for Expected Introduction Concentration (EIC) for the Environmental Assessment.

The estimated annual consumption of estradiol for the entire Alora product line is [redacted] This includes the three approved sizes and the proposed 9 cm^2 size. In accordance with the FDA guidance document *Environmental Assessment of Human Drug and Biologics Applications* (July 1998), the EIC is:

[redacted]

which is well below the guidance document's minimum threshold of 1 ppb.

B. Dr. Chikale requested clarification regarding Watson's intentions for the use [redacted] in the drug product formulation.

Watson does not intend to use [redacted] in the product formulation.

We trust this provides sufficient information to permit continued review of this NDA. If you have any questions or need any additional information, please feel free to contact me by telephone at (801) 588-6200 or by fax at (801) 583-8135.

Best Regards,

Dorothy A. Frank

Dorothy A. Frank, M.S., R.A.C.
Executive Director, Proprietary Regulatory Affairs

Patent Information Certification

In accordance with 21 CFR § 314.53 (d) (2) ii, Watson Laboratories, Inc. is providing the following identification of patents that claim our drug product Alora® Estradiol Transdermal Systems, which are the subject of this application to add a new indication.

Patent Number (Exp. Date)	Title	Patent Owner
5,122,383 (5/17/2011)	Sorbitan Esters as Skin Permeation Enhancers	Watson Pharmaceuticals, Inc.
5,164,190 (12/11/2010)	Subsaturated Transdermal Drug Delivery Device Exhibiting Enhanced Drug Flux	Watson Pharmaceuticals, Inc.
5,212,199 (5/17/2011)	Sorbitan Esters as Skin Permeation Enhancers	Watson Pharmaceuticals, Inc.
5,227,169 (5/17/2011)	Sorbitan Esters as Skin Permeation Enhancers	Watson Pharmaceuticals, Inc.

Dorothy A. Frank Date: 12 January 2001

Dorothy Frank
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-310 SUPPL #

Trade Name Alora Generic Name Estradiol Transdermal System

Applicant Name Watson Laboratories, Inc. HFD- 510

Division Division of Metabolic and Endocrine Drug Products

Approval Date April 5, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)?

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical

data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 21-167, 20-323/S-023
Vivelle (estradiol transdermal system)

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /__/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 1996023 "A Randomized, Double-Blind, Placebo-Controlled, 24-Month, Dose-Ranging, Multi-Center Study Comparing EMTDS to Placebo in the Prevention of Bone Loss in Hysterectomized Postmenopausal Women"

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more

investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_1_, Study # _1996023 "A Randomized, Double-Blind, Placebo-Controlled, 24-Month, Dose-Ranging, Multi-Center Study Comparing EMTDS to Placebo in the Prevention of Bone Loss in Hysterectomized Postmenopausal Women"_

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the

conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____

_____	!	_____
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

cc:
Archival NDA
HFD-510/Division File
HFD-510/RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

David Orloff
4/5/02 01:16:13 PM

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Debarment Certification

(FD&C Act 306(k)(1))

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Debarment Certification

Watson Laboratories, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Sec. 306(a) or (b) of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Dorothy A. Frank

Date: 12 January 2001

Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs

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Financial Information

(21 CFR 314.50 Part 54)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Protocol 1996023

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical investigators	
See Attached List	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Dorothy Frank	Director, Regulatory Affairs
FIRM/ORGANIZATION	
Watson Laboratories, Inc.	
SIGNATURE	DATE
Dorothy A. Frank	04 December 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address in the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14[illegible]
Rockville, MD 20857

FORM FDA 3454 (3/99)

WITHHOLD 4 PAGE (S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 11, 2002

TO: File
NDA 21-310, Alora® (estradiol transdermal system)

FROM: Samuel Wu, Regulatory Project Manager

SUBJECT: **Safety Update**

The firm responded to our November 16, 2001, approvable letter on November 19, 2001. However, there was no information on safety update included in the submission, as requested in the approvable letter.

In the November 15, 2001, submission, firm stated that there were no ongoing studies for the osteoporosis indication and thus no further safety data would be available. This submission satisfies the requirement for submitting safety update in response to our November 16, 2001, approvable letter.

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/s/

Samuel Wu
3/28/02 02:53:03 PM
CSO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-310

FEB 19 2002

Watson Laboratories, Inc.
Attention: Dorothy A. Frank, M.S., R.A.C.
Executive Director, Proprietary Regulatory Affairs
417 Wakara Way
Salt Lake City, UT 84108

Dear Ms. Frank:

We acknowledge receipt on February 6, 2002, of your February 5, 2002, resubmission to your new drug application (NDA) for Alora (Estradiol Transdermal System), 0.025 mg/day, 0.05 mg/day, and 0.075 mg/day.

This resubmission contains additional labeling information submitted in response to our January 18,2002, approvable letter.

We consider this a complete class 1 response to our action letter. Therefore, the user fee goal date is April 6, 2002.

If you have any questions, call me at 301-827-6416.

Sincerely,

{See appended electronic signature page}

Samuel Y. Wu, Pharm.D.
Regulatory Project Management
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Samuel Wu
2/19/02 04:42:13 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-310

Watson Laboratories, Inc.
Attention: Dorothy A. Frank, M.S., R.A.C.
Executive Director, Proprietary Regulatory Affairs
Research Park
417 Wakara Way
Salt Lake City, UT 84108

Dear Ms. Frank:

We acknowledge receipt on November 20, 2001, of your November 19, 2001, resubmission to your new drug application (NDA) for Alora (Estradiol Transdermal System), 0.025 mg/day, 0.05 mg/day, and 0.075 mg/day.

This resubmission contains additional labeling information submitted in response to our November 16, 2001, approvable letter.

We consider this a complete class 1 response to our action letter. Therefore, the user fee goal date is January 20, 2002.

If you have any questions, call me at 301-827-6416.

Sincerely,

{See appended electronic signature page}

Samuel Y. Wu, Pharm.D.
Regulatory Project Management
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Samuel Wu
11/30/01 11:43:59 AM

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 20, 2001

TO: NDA 21-310

FROM: Randy Hedin

SUBJECT: User Fee for NDA 21-310, Alora (estradiol transdermal system)

I spoke with Cherri Petrie, Manager, Regulatory Affairs, of Watson Laboratories, a variety of times during the past two weeks concerning the user fee submitted for NDA 21-310. I also referred to conversations between her and Mike Jones of the FDA in September of 2000, in which it was discussed if the application should be a supplement, a type 6 NDA, or a type 3 NDA, and the user fee ramifications for each. It was stated at that time, because Watson Laboratories has an approved application for Alora and per our bundling policy, they could submit the application as a supplement and pay the supplement fee (both the strength and indication would be bundled). However, for our own administrative convenience, we would like a new NDA submitted to the Division of Metabolic and Endocrine Drug Products, and we would assess a supplement fee for the new NDA.

I explained to Ms. Petrie that what was not brought up in the September 2000, conversation is that the firm is seeking [redacted] A treatment study is the only study submitted in the NDA. [redacted] The firm submitted an amendment to the NDA on February 14, 2001, withdrawing the [redacted] (see attached letter).

APPEARS THIS WAY
ON ORIGINAL

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

February 14, 2000

John K. Jenkins, M.D., Director
Division of Metabolic and Endocrine
Drug Products (HFD- 510)
CDER, Document Room 14-B-19
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-310 Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

Dear Dr. Jenkins:

In accordance with the Federal Food, Drug, and Cosmetic Act, Watson Laboratories, Inc. is submitting an amendment to our New Drug Application for a new system size and indication for Alora Estradiol Transdermal Systems. Alora is also subject of our NDA — that was reviewed and approved by the Division of Reproductive and Urologic Drug Products. Three dosage strengths, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day are approved in NDA — for the treatment of moderate to severe vasomotor symptoms associated with menopause.

This amendment is submitted to withdraw the words " —— ;" from the indication proposed in our original submission for 0.025 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day Alora Estradiol Transdermal Systems. The new proposed indication is "prevention of postmenopausal osteoporosis".

If you have any questions or need any additional information, please feel free to contact me by telephone at (801) 588-6200 or by fax at (801) 583-8135.

Sincerely,

Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs

Desk copy: Randy Hedin

Research Park, 417 Wakara Way, Salt Lake City, UT 84108 • Tel: 801/588-6200 • Fax: 801/583-6042

/s/

Randy Hedin
2/20/01 04:01:52 PM
CSO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-310

Watson Laboratories, Inc.
Attention: Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs
417 Wakara Way
Salt Lake City, Utah 84106

Dear Ms. Frank:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Alora® (estradiol transdermal system) 0.025 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day
Review Priority Classification:	Standard (S)
Date of Application:	January 12, 2001
Date of Receipt:	January 16, 2001
Our Reference Number:	NDA 21-310

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 17, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be November 16, 2001, and the secondary user fee goal date will be January 16, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632).

We note that you have requested a waiver of the pediatric study requirement. We will make a determination whether to grant or deny the request during the review of the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Randy Hedin
1/23/01 12:33:19 PM

APPEARS THIS WAY
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Meeting Date: February 28, 2001 Time: 11:00 - 11:30 PM Location: 17B-43

NDA 21-310 Alora (estradiol transdermal system)

Type of Meeting: Filing Meeting

External participant: None

Meeting Chair: Dr. Colman

External participant lead: None

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Eric Colman, M.D., Clinical Team Leader, DMEDP
Patricia Beaston-Wimmer, M.D., Ph.D., Clinical Reviewer, DMEDP
Karen Davis-Bruno, Ph.D., Pharmacology Team Leader, DMEDP
Hae-Young Ahn, Ph.D., Team Leader, OCPB
Robert Shore, Ph.D., Reviewer, OCPB
Elsbeth Chikhale, Ph.D., Reviewer, DNDCII
Todd Sahlroot, Ph.D., Team Leader, DOBII
Dornette Spell-Lesane, Regulatory Project Manager, DRUDP
Randy Hedin, R.Ph. Senior Regulatory Management Officer, DMEDP

External participant Attendees and titles:

None

Meeting Objectives:

To determine if NDA 21-310 will be filed, and discuss plans for the review of the NDA.

Discussion Points:

- Chemistry: The application is fileable.
- Pharmacology not The application is fileable. However, preclinical data has been submitted for review.
- Biopharm: The application is fileable.

- Statistics: The application is fileable.
- Clinical: The application is fileable.

Decisions (agreements) reached:

- The application will be filed.
- The application does contain financial disclosure information.
- The review will be done as a standard review. The goal to finish the reviews with team leader sign-off is October 9, 2001.
- The application will not be discussed at an Advisory Committee meeting.
- A DSI audit will not be requested.
- The user fee goal dates are:
  - 10 Month: November 16, 2001
  - 12 Month: January 16, 2002

Unresolved or issues requiring further discussion:

- None

Action Items:

- Schedule status meetings as appropriate.

Signature, minutes preparer:_____

Concurrence Chair:_____

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/s/

Randy Hedin
4/9/01 10:29:04 AM

Eric Colman
4/18/01 08:13:18 AM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA #: 21-310 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: January 16, 2001 Action Date: AP: April 5, 2002

HFD 510 Trade and generic names/dosage form: Alora (estradiol transdermal system)

Applicant: Watson Laboratories, Inc. Therapeutic Class: Estrogens

Indication(s) previously approved:
1. Treatment of moderate-to-severe vasomotor symptoms associated with the menopause.
2. Treatment of vulvar and vaginal atrophy.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Prevention of postmenopausal osteoporosis

Is there a full waiver for this indication (check one)?

✓ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
✓ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed

☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Samuel Y. Wu, Pharm.D.
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Samuel Wu
4/8/02 02:02:18 PM
CSO

Samuel Wu
4/8/02 02:05:50 PM
CSO

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MEDICAL TEAM LEADER MEMORANDUM

DATE: October 12, 2001

NDA: 21-310

DRUG: Alora (transdermal 17β-estradiol)

INDICATION: Prevention of postmenopausal osteoporosis

COMPANY: Watson

PRIMARY REVIEWER: Patricia Beaston-Wimmer, MD, PhD

Background

Transdermal Alora, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day, is currently approved for the treatment of moderate-to-severe vasomotor symptoms associated with the menopause, the treatment of vulval and vaginal atrophy, and the treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. In this supplemental NDA, Watson is seeking approval of 0.025 mg/day, 0.05 mg/day, and 0.075 mg/day of Alora for the prevention of postmenopausal osteoporosis (PMO). In support of approval, the company conducted a 2-year, randomized, double-blind, placebo-controlled trial of postmenopausal women with lumbar spine (LS) bone mineral density (BMD) as the primary endpoint.

Overview of Clinical Trial

Three hundred fifty-five postmenopausal (natural or surgical), hysterectomized women, aged 26 to 69 years, with a mean LS T-score of –0.64 (range –2.7 to 3.8) were randomized in equal fashion to one of four treatment groups: placebo or Alora 0.025 mg/day, 0.05 mg/day, or 0.075 mg/day. All subjects received 1000 mg/day of oral calcium supplementation. The primary endpoint was the change from baseline to Year 2 in LS BMD, the standard endpoint for estrogens seeking a prevention of PMO indication.

There were no statistically significant differences between the Alora and placebo groups for baseline demographic characteristics. Eighty-seven percent of the women were Caucasian, the mean age was about 53 years, the average BMI was 28.5 kg/m^2, the average number of years since hysterectomy was 16, and the mean baseline LS T-score was –0.6. Approximately 67% of placebo-treated subjects and 50% of Alora-treated subjects completed the 2-year study. Over 80% of placebo subjects had at least one post-baseline BMD measurement, while about 70% of the Alora-treated women had at least one on-study BMD assessment. Protocol violations were evenly distributed among the treatment groups and were unlikely to have affected the primary outcome of the study.

In the assessment of the change in LS BMD from baseline to Endpoint, the placebo group had a mean percent decrease in BMD of 0.8%, whereas the Alora 0.025 mg/day, 0.05 mg/day, and 0.075 mg/day groups had mean percent increases of 1.4%, 3.4%, and 4.2%, respectively ($p<0.01$ for all comparisons of Alora vs. placebo). The placebo-subtracted changes in LS BMD for the Alora groups are similar to equivalent doses of other approved transdermal estrogens.

Aside from a higher incidence of moderately severe application site skin reactions in the Alora vs. placebo groups, the reporting of clinical adverse events was what one would expect for a transdermal estrogen product (i.e., breast pain). There were no significant differences between active- and placebo-treated groups in the reporting of laboratory abnormalities or vital signs.

Comment

Watson has provided adequate data to support approval of 0.025 mg, 0.050 mg, and 0.075 mg/day of their transdermal 17β-estradiol, Alora, for the prevention of PMO. Compared with placebo, there was a more-or-less dose-related increase in LS BMD in the active-treatment groups, with the lowest dose (0.025 mg) increasing mean LS BMD by approximately 2.0%.

In hindsight, there were three features of the Alora clinical trial that were less than ideal. First, some of the women had non-osteopenic LS BMD values (i.e., greater than –1.0). It would have been more appropriate to limit the inclusion of women with T-scores in the osteopenic range (-1.0 to –2.5). Second, all of the study participants had undergone an hysterectomy; therefore, there was no need to study the effect of Alora plus a progestin on BMD. Progestins may attenuate the affect of estrogens on BMD – this will be pointed out in the labeling. And third, the 1000 mg per day supplementation of calcium was probably sub-optimal for most study subjects. None of these facts preclude approval of Alora, however.

In anticipation of reaching agreement with Watson on final labeling, I, like Dr. Beaston-Wimmer, recommend that the 0.025 mg, 0.05 mg, and 0.075 mg/day doses of Alora be approved for the prevention of PMO.

Eric Colman, MD

I concur Dr. Colman's recommendation

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APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Colman
10/17/01 02:20:49 PM
MEDICAL OFFICER

David Orloff
10/22/01 04:28:25 PM
MEDICAL OFFICER
Concur with Drs. Colman and Beaston-Wimmer. There will be no separate Division Director memo. DGO